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EDITORIAL COMMENT

Mineralocorticoid Receptor Antagonists in Patients With End-Stage Renal Disease on Chronic Hemodialysis*

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Chronic kidney disease (CKD) is a public health priority. The unadjusted mortality rate of end-stage renal disease (ESRD) is 29% at 2 years and 52% at 5 years. ESRD is associated with cardiovascular (CV) morbidity and mortality 2 to 10 times that of a population with normal renal function. Heart disease is the leading cause of mortality in patients on hemodialysis (HD) (42% of total mortality) (1).

See page 528

Despite these observations few pharmacological treatments are evidence based because CKD patients on HD are usually excluded from CV prevention trials. Two trials including patients with ESRD on HD showed that statins had no effect (2,3). Aside from 2 positive studies among patients with ESRD on HD with heart failure and impaired left ventricular ejection fraction (stage III/IV) in which a beta-blocker (4) or a combination of an angiotensin-converting enzyme inhibitor (ACE-I) with an angiotensin II receptor blocker (ARB) (5) was used, FOSIDIAL (the Fosinopril in Dialysis study), which was the largest (n = 397) CV event trial using an antihypertensive agent that included patients with ESRD on HD with left ventricular hypertrophy, showed that an ACE-I did not achieve statistical significance (6). However, a meta-analysis encompassing 6 trials with 1,202 patients (30% of which were FOSIDIAL patients), suggested that antihypertensive drugs as a whole may improve CV outcomes in patients with ESRD on HD (7).

In patients with heart failure without severe CKD on an ACE-I or ARB and/or a beta-blocker, the mineralocorticoid receptor antagonists (MRAs) spironolactone and eplerenone have shown a reduction in CV events (8–10). The beneficial effects of MRAs may involve cardiovascular remodeling, including collagen turnover (11), as well as effects on oxidative stress and endothelial and immune functions (12). Moreover, recent experimental data suggest that aldosterone may be involved in vascular calcification, a prominent feature of vascular aging and CV morbidity in patients with CKD (13). MRAs have also been shown to reduce mesangial fibrosis, to prevent podocyte damage, and to reduce albuminuria (14). A randomized controlled trial conducted in the early stages of CKD showed that adding spironolactone to an ACE-I or ARB reduced left ventricular mass and arterial stiffness, which are independent predictors of CV events in patients with ESRD (15).

Most clinicians are, however, reluctant to use MRAs in patients with chronic heart failure, especially in those with CKD, because of the risk of hyperkalemia. MRAs are currently contraindicated in patients with an estimated glomerular filtration rate <30 ml/min/1.73 m^2, including patients on HD. However, recent clinical studies have demonstrated the safety (especially in regard to hyperkalemia) of MRAs in ESRD patients on HD (16). Several studies also suggest a cardiovascular protective effect while assessing surrogates such as intima-medial thickness, left ventricular mass (16), or calcifications (17).

In this issue of the *Journal,* Matsumoto et al. (18) report the results of the first open-label, randomized trial evaluating CV and cerebrovascular events in patients with ESRD on HD (DOHAS [Dialysis Outcomes Heart Failure Aldactone Study]) comparing the MRA spironolactone (25 mg/day) to usual care in 309 oligoanuric patients followed up for 3 years. Strikingly, both the primary and secondary outcomes were significantly reduced. The composite of death from CV and cerebrovascular events or hospitalization for CV and cerebrovascular events (primary outcome) was 5.7% (n = 9) in the treatment group and 12.5% (n = 19) of patients in the control group, with a hazard ratio (HR) for treatment of 0.404 (95% confidence interval [CI]: 0.202 to 0.809; p = 0.017), while death from all causes (secondary outcome) was 6.4% (n = 10) versus 19.7% (n = 30) (HR: 0.355; 95% CI: 0.191 to 0.662; p = 0.002). Three patients (1.9%) discontinued spironolactone treatment because of serious hyperkalemia.

Matsumoto et al. should be congratulated for addressing the neglected issue of CV events in HD patients and for incorporating an MRA as a potential therapy in these high-risk patients. As acknowledged by the authors, DOHAS is not the definitive pivotal trial to change clinical practice. They rightly state that: "First, this study was not blinded. Further, a placebo was not administered to the control group.

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Additionally, the interaction tests were underpowered, and the number of endpoints was small." Moreover, owing to the low recruitment rate due to participation refusal (only 309 patients were included vs. the scheduled sample size of 600 patients required to demonstrate a 40% reduction of all-cause death for a 2-sided alpha level of 0.05, with 80% power), the external validity of this study will require further confirmation. The applicability of the results to patients on HD with residual diuresis is also uncertain because only oligoanuric patients were studied. The results are, however, sufficiently provocative to encourage further large-scale, multicenter, randomized, double-blind, placebo-controlled trials necessary to provide a definitive answer as to the role of MRAs in patients with ESRD on HD. Fortunately, such a trial is underway. ALCHEMIST (ALdosterone Antagonist Chronic HEModialysis Interventional Survival Trial; NCT01848639) is underway and plans to recruit 825 patients with the primary endpoint of the time to onset of the first incident (nonfatal myocardial infarction or hospitalization for heart failure or nonfatal stroke or CV death). Thus, the results of DOHAS and ALCHEMIST hold the promise of a reduction in CV events in these high-risk patients with ESRD on HD.

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